REMARKS

The Rejections

Claim Rejections - Non-Statutory Double Patenting

Claims 73-86 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1-177 of copending Application No. 09/159,105 (see WO 99/14998) or continuation/divisional thereof, in view of Feghali et al. Medline 98242495. Claims 1-177 (particularly claims 4, 116, and 118) are said to be drawn to treatment of sensorineurotrophic hearing loss which is one of the neurological disorders generically embraced by the instant claims, as evidenced by Feghali that sensorineural hearing loss is a neurological disorder treatable by neurotrophic factors. The neurotrophic factors of SN 09/159,105 generically embraced the instantly claimed compounds.

Applicants respectfully request that this rejection be held in abeyance until such time as the '105 patent application is allowed and issues as a patent, and claims in the instant application are found to address allowable subject matter. At that time, any allowed and issued claims should be examined with regard to the instant pending claims. Applicants would at that time submit an appropriate terminal disclaimer, if and as warranted.

In the meantime, Applicants note for the record their disagreement with the rejection even at the present time. Most of the claims of the '105 application are far broader than th instant pending claims. There is nothing of record that indicates that the broad claims

relating to treatment of sensorineural hearing loss would lead one of ordinary skill in the art to expect that the specific instant group of compounds would be useful in treating neurological disorders specifically by stimulating growth of damaged peripheral nerves or promoting neuronal regeneration. At best, the '105 claims may be considered to support a conclusion that the instant claimed inventions may be obvious to try, but not obvious.

Feghali discusses the potential use of neurotrophic factors to treat sensorineural hearing loss. Such hearing loss, however, is specifically ascribed by Feghali to relate to hair cell damage and loss of auditory hair cells. Again, there is nothing of record that would lead one of ordinary skill to believe that compounds useful as suggested in Feghali would be useful in treating neurological disorders specifically by stimulating growth of damaged peripheral nerves or promoting neuronal regeneration.

Applicants respectfully request that this rejection be reconsidered and withdrawn, or at least held in abeyance until allowable claims are determined.

Claim Rejections - 35 U.S.C. § 103(a) or Non-Statutory Double Patenting

Claims 73-86 are provisionally rejected under 35 U.S.C. § 103(a) or under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the reference of the claims of Hamilton U.S. Pat. No. 5,801,187, or 5,846,979, or 6,218,423, or 6,274,607 in view of SN 09/159,105 and Feghali et al. The Hamilton patents are said to disclose and claim the instant method of treating neurological disorder with n urotrophic compounds. See '187 claims 15-16 and col. 5, lines 30-32 compounds; '979 claims 1-37 and generic variation of tr atable disorders at col. 7, line 59 to col. 8, line 21;

'423 claims 17-20; or '607 claims 9-12. The Hamilton patents are said to disclose all the elements of the claims except the neurotrophic agent are structurally analogous to the claimed compounds. SN 09/159,105 taught in claims 1-177 analogous treating of neurotrophic hearing loss, the '187, '979, '423, and '607 compounds/neurotrophic agents are alternative choices for the instantly claimed compounds. The office action states that one of ordinary skill would be motivated to employ a structurally similar known alternative for the generic neurotrophic factor related pathology as the instant claims.

Preliminarily, Applicants note that the rejections appear to have criss-crossed three or four of the references. Present patent counsel only recently received this file, or w would have called the Examiner promptly to try to clarify the rejection. Specifically, while '187 patent only has claims 1-12, the rejection references claims 15-16 and col. 5, lines 30-32 compounds. The '979 patent only has claims 1-20, though the rejection cites claims 1-37 and generic variation of treatable disorders at col. 7, line 59 to col. 8, line 21. Also cited are the '423 claims 17-20; or '607 claims 9-12.[1] As much as possible, applicants will generally address all the potentially relevant claims in the cited references. Should this rejection be maintained, Applicants respectfully request that it be clarified.

Further, Applicants respectfully request that this rejection be held in abeyance until such time as allowable subject matter is identified in the present application, and claims are allowed. At that time, the allowed claims should be examined with regard to the referenced

[1] The apparent confusion involves at least three of the patents, because neither the '187 nor the '979 patent has 37 claims. Thus, we could not readily ascertain exactly which claims were intended to be cited for each reference.

patents. If and as appropriate at that time, Applicants would submit a suitable terminal disclaimer.

In the meantime, Applicants respectfully disagree for the record. First, the instant claims all address methods of treating a neurological disorder, comprising administration of a compound according to the recited formula in order to stimulate growth of peripheral nerves or to promote neuronal regeneration. In contrast, most of the cited claims broadly relate to methods of effecting a neuronal activity, or treating particular disorders, without any reference to a particular mechanism of efficacy. There is absolutely no basis in the art of record to conclude that one of ordinary skill in the art would consider that the instant compounds would be particularly useful for treating neurological disorders specifically by stimulating growth of peripheral nerves or promoting neuronal regeneration.

Further, the structure of the compounds used in the instant claims is distinguishable from the compounds in the cited references.

For example, in the instant claims, the heterocyclic ring is a pyrrolidine. In each of the claims, the substituent connected to the carbon adjacent the nitrogen in the pyrrolidine ring is selected from the group consisting of a bond, C_1-C_{10} straight or branched chain alkylene, ethylene, and butylene, which substituent is then further connected to a carboxylic acid or carboxylic acid isostere. Thus, the ring carbon is generally not attached to an ester, ketone, amide, thioester, or -CSSR.

In contrast, the claims of the '187 patent all reference compounds wherein the ring is not a pyrrolidine, but instead is a thiazole or isothiazole ring. And the substituent

connected to the carbon adjacent to the ring's nitrogen is always an ester. The claims of the '979 patent reference compounds wherein the ring is a pyrrolidine, piperidine, or azepine ring. The carbon adjacent the nitrogen in the ring is always attached to an ester, ketone, amide, or thioester. The '423 patent claims reference compounds in which the ring is a pyrrolidine, and the carbon adjacent the nitrogen is attached to an ester, ketone, or amide. And the claims of the '607 patent reference compounds in which the ring is a thiazole or isothiazole ring. The ring carbon adjacent to the nitrogen is attached to a carbonyl or thiocarbonyl which is part of a thioester (-COSR-) or -CSSR. Thus, there is no overlap between the compounds in the instant claims, and the claims cited. Accordingly, and especially without any motivation in the record to use the instant compounds as claimed, there is no basis in the cited claims for one of ordinary skill in the art to expect that the specific compounds of the instant claims would provide the claimed effect.

The cite to Hamilton SN 09/159,105 adds little of substance to the record. Even if the '105 claims taught that the cited compounds/neurotrophic agents are alternative choices for treating neurotrophic hearing loss, there is no basis to conclude that one of ordinary skill in the art would necessarily expect the particular compounds in the instant claims to treat neurological disorders specifically by stimulating growth of peripheral nerves or promoting neuronal regeneration. At most, Hamilton might make the instant specific inventions obvious to try, rather than obvious. But the instant claims are not obvious. And there is absolutely no motivation in the cited prior art to use the specific compounds as claimed.

Thus, one of ordinary skill in the art would not expect from the cited references that the compounds in the instant claims would provide the claimed results. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 73-86 are rejected under 35 USC § 112, second paragraph, as being indefinite. The scope of the claims is said to be unclear. "Are they 'carboxylic acid' and carboxylic acid isosteres? Or are they including 'carboxylate' also. Please note that the cyclic moieties and isosteric structures in claim 73 included both 'carboxylic acid' and 'carboxylate' i.e. esters, amides etc." The office action states that it is clearly known in the art that "carboxylic acid" bioisosteres are distinct from "carboxylate" and that the concept has been well taught in the art, citing King p. 208 and Patani p. 3163-64 and 3169. The claims included in the term "carboxylic acid isostere" choices of ester and amides are self contradictory and confusing.

Applicant respectfully disagrees. In context, and in light of the specification, one of ordinary skill in the art would understand what is meant by the claim terms "carboxylic acid isostere" or "carboxylic acid or carboxylic acid isostere." Further, the Examiner points only to confusion in claim 73. Accordingly, claims 80-86 should not be considered to be affected by this rejection.

In claim 73, the term "carboxylic acid or carboxylic acid isostere" would be clearly understood by one of ordinary skill in the art. This term, in context, refers to carboxylic acid or an isostere of carboxylic acid, optionally substituted as claimed. The term "carboxylic

acid isostere" would be clearly understood, in context, to one of ordinary skill in the art -- isosteres of carboxylic acid, potentially substituted as claimed. The term "isostere" is a term of art, which would be readily understood by one of ordinary skill in the art. And an isostere would normally be "of" a particular moiety. Hence, a "carboxylic acid isostere" would readily be understood to refer to an isostere of carboxylic acid. Thus, this term would be readily understood by one of ordinary skill in the art.

King and Patani are consistent with this position. For example, the office action notes that carboxylic acid bioisosteres are distinct from carboxylate. However, the same moiety can be an isostere to more than one other moiety. For example, King at 208 notes that, as ring equivalents, -S- can serve as an isostere of -CH=CH-, or it can serve as an isostere of -O-, or -NH-. As a bivalent isostere, -S- correlates to -NH-, -O-, or $-CH_2-$. Similarly, Patani at 3168 discusses various types of carboxylate group bioisosteres -- replacements of only the hydroxyl portion, or of both the hydroxy and carboxyl fragments. In fact, and of particular relevance, Table 43 of Patani, on page 3168, lists both carboxylic acid and carboxylate as "carboxylic acid bioisosteres."

Thus, while the term isostere is readily understood by one of ordinary skill in the art, there is inherently some degree of flexibility in determining exactly what is a isostere for a particular fragment. Nevertheless, in context, one of ordinary skill in the art would readily understand the terms of the instant claims, and the intended scope of the terms in those claims.

Applicants respectfully request that this r jection b r considered and withdrawn.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 73-86 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hamilton U.S. 5,801,187 in view of King or Patani. Claims 73-86 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9-12 of the '187 patent, in view of King or Patani. The office action notes that the "carboxylate" isosteres are prima facie obvious over the prior art. The replacement of a carboxyl or carbonyl moiety of a biologically active compound with a conventional "bioisosteric replacement" is said to be prima facie obvious because artisan in the field would recognize that such modification is a rational approach in drug design to gain more useful compounds, and would expect to use such for the same methods as in claims 9-12 of the '187 patent.

Applicants respectfully disagree. First, the Examiner sets forth what might be a perfect argument that the instant claims may be "obvious to try," though they are not obvious over the prior art. Second, there is no motivation provided by the prior art to make the specific inventions embodied by the instant claims. Third, the particular use claimed is not obvious from the use disclosed in the prior art of record.

Especially when using non-classical isosteres, such as many of the isosteres suggested in the instant claims, there is certainly no guarantee that an isostere will produce the desired effect. Because of the complexities of molecular structure and bioactivity generally, clearly there may at least be significant changes in selectivity, toxicity, and metabolic stability wh n an isostere is substituted in an active compound. See, e.g., King

at 207. For example, Patani at 3163 reports failing "to identify a more potent bioisostere because of the inability to attain optimal binding geometry." Thus, while isosteric substitutions may present modifications that are obvious to try alternatives, one of ordinary skill in the art would not expect or assume that a particular isostere necessarily would produce the desired efficacy. In effect, the use of isosteres presents the researcher with 'educated guesses" in an attempt to find further active compounds. But isosteres do not by themselves present any reasonable concrete expectation that they will provide the desired results.

Second, there is absolutely no motivation or incentive in the cited art for one of ordinary skill in the art to prepare and use the claimed compounds for the claimed efficacy and mechanism. A prima facie case of obviousness requires that the prior art provide some suggestion or incentive to make the claimed substitution. *In re Grabiak*, 769 F.2d 729, 731-32, 226 U.S.P.Q. 870, 872 (Fed. Cir. 1985). Here, there is no suggestion regarding either the particular compounds or the specific mechanism of efficacy.

Further, the structure of the compounds used in the instant claims is distinguishable from the compounds in claims 9-12 of the '187 patent. For example, in the instant claims, the heterocyclic ring is a pyrrolidine. In each of the claims, the substituent connected to the carbon adjacent the nitrogen in the pyrrolidine ring is selected from the group consisting of a bond, C_1-C_{10} straight or branched chain alkylene, ethylene, and butylene, which substituent is then further connected to a carboxylic acid or carboxylic acid isostere. Thus, the ring carbon is generally not attached to an ester.

In contrast, the claims of the '187 patent all reference compounds wherein the ring is not a pyrrolidine, but instead is a thiazole or isothiazole ring. And the substituent connected to the carbon adjacent to the ring's nitrogen is always an ester. Thus, there is no basis in the cited claims for one of ordinary skill in the art to expect that the particular compounds of the instant claims would provide the claimed effect.

Third, as discussed above, the instant claims address methods of treating a neurological disorder, comprising administration of a compound according to the recited formula in order to stimulate growth of peripheral nerves or to promote neuronal regeneration. In contrast, the claims of the '187 patent broadly relate to methods effecting neuronal activity. There is no basis in the art of record to conclude that one of ordinary skill in the art would consider that the instant compounds specifically would be particularly useful for treating neurological disorders specifically by stimulating growth of peripheral nerves or promoting neuronal regeneration. And as discussed above, King and Patani simply offer "obvious to try" alternatives, rather than alternatives that one of ordinary skill in the art would expect necessarily to be able to use successfully.

Thus, one of ordinary skill in the art would not expect from any combination of the cited references that the compounds in the instant claims would provide the claimed results. Applicants respectfully request that this rejection be reconsidered and withdrawn.

CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to b nov l and patentably distinguishable over the prior art of record. Th Examiner is

therefore respectfully requested to reconsider and withdraw the rejections of record, and to issue a Notice of Allowance.

The Examiner is welcome to telephone the undersigned attorney directly if warranted, here in Washington, D.C. at (202) 974-6004.

Respectfully submitted,

LYON & LYON LLP

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By: _____
Scott H. Blackman
Reg. No. 34,088

633 West Fifth Street, Suite 4700
Los Angeles, California 90071-2066